UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,169	02/12/2002	Carl T. Wittwer	7475-70049	5884

49437 7590 05/23/2005

ROCHE
11 SOUTH MERIDAN STREET
INDIANAPOLIS, IN 46204

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,169	WITTWER, CARL T.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Priority

1. Applicant's claim for priority under 35 U.S.C. 120 is acknowledged. However, the parent application from which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-10 of this application. Specifically, there is no support for the final step of claim 1, where "if the call is positive, confirming the positive call by a melting temperature analysis" in the parent application. Therefore, the claims receive a priority date of February 12, 2002.***Double Patenting***

2. Claims 1, 3-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,387,621 in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Claims 1-2 of U.S. Patent No. 6,387,621 teach a method for determining the presence of a nucleic acid comprising the

steps of

(a) providing a fluorescent entity capable of indicating the presence of the nucleic acid and capable of providing a signal related to the quantity of the

nucleic acid,

(b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity,

(c) measuring fluorescence intensity of the fluorescent entity at each of the plurality of amplification cycles to produce a fluorescent value for each cycle related to the quantity of the nucleic acid present at each cycle,

(d) generating a fluorescence-verses-amplification-cycle plot wherein the fluorescent values are recorded for each amplification cycle,

(e) calculating slopes of segments of the fluorescence-verses-amplification-cycle plot using a plurality of the fluorescent values, using the segment slopes of the fluorescence-verses-amplification-cycle plot to establish a baseline fluorescence region by generating a slope value for each of a plurality of the amplification cycles, and establishing the baseline fluorescence region comprising an interval of cycles that includes the amplification cycle with the slope value having an absolute value closest to zero, and ascertaining whether the fluorescence value during a selected amplification cycle is outside the baseline fluorescence region.

With regard to claim 3, Claims 1-24 of U.S. Patent No. 6,387,621 do not require an internal standard.

With regard to claim 10, Claim 13 of U.S. Patent No. 6,387,621 teaches the automated method.

Claims 1-24 of U.S. Patent No. 6,387,621 do not teach confirmining the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or maxima based upon the dF/dT derivative melting curves (see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

With regard to claims 8 and 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Claims 1-24 of U.S. Patent No. 6,387,621 since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis with a melting point analysis in order to perform a variety of checks, including multiplex genotyping, internal controls and internal competitors as standards. Further, it would have been prima facie obvious to

combine Hermann with any analytical PCR method to improve the specificity and validity of the method for the reasons cited from the Hermann paper. This additional verification solves the problem, recognized by U.S. Patent No. 6,387,621 that " accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16)" The specification continues, noting "Automatic identification of the background is surprisingly difficult. (see column 6, lines 48-49)." Hermann provides one solution for this problem by providing a means to accurately discriminate between positive and negative PCR samples such as those used by U.S. Patent No. 6,387,621 which would further support the determination made by the analytical method of U.S. patent 6,387,621.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer et al (EP 1059523 A2) in view of Herrmann et al (Clin. Chem. (2000) 46(3):425-428).

Wittwer teaches a method, which uses automated processes such as a fluorometer and computer for plotting (see column 6, paragraph 0022), for determining the presence of a nucleic acid (see abstract) comprising the steps of:

a) providing a fluorescent entity, SYBR Green dye, which is capable of providing a signal indicating the presence and amount of a nucleic acid (see column 5, paragraph 0019),

b) amplifying the nucleic acid through a plurality of amplification cycles in the presence of the fluorescent entity, SYBR green acid (see column 5, paragraph 0019),

c) measuring the fluorescence of the fluorescent entity during each of the plurality of amplification cycles acid (see column 5, paragraph 0019),

d) generating a plot wherein the fluorescent values are recorded for each amplification cycle (see figure 5, for example

e) performing a confidence band analysis by calculating slopes of segments of the plot using a plurality of the fluorescent values, using the segment slopes of the plot to establish a baseline nuorescence region by generating a slope value for each of a plurality of the amplification cycles, and establishing the baseline florescence region comprising an interval of cycles that includes the amplification cycle with the slope value having an absolute value closest to zero, outputting a positive result if the fluorescence value of a selected amplification cycle is outside the baseline fluorescence region (see figure 5, columns 8-10 and claims 2-14).

With regard to claim 3, Wittwer teaches that the baseline is established without the use of an internal standard (see columns 9-10).

Wittwer does not teach confirming the results by a melting temperature analysis.

Herrman teaches performing a PCR reaction followed by confirming the target using a melting temperature analysis (see page 425, column 2).

With regard to claim 4, Hermann teaches obtaining a melting profile (see figure 1), determining the minima or maxima based upon the dF/dT derivative melting curves

(see figure 1 and page 427, column 1) and comparing the Tm with the known Tm (see figure 1 and page 427, column 1).

With regard to claims 5-7, Hermann teaches performing the method subsequent to amplification, but MPEP 2144.04 notes "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results" In this case, with regard to claims 5 and 6, the monitoring step is identical to that performed after amplification and would have been expected to function in the same way during amplification, with the variation simply being an increasing amount of target available to the probe as amplification proceeds, so the order of the steps is prima facie obvious.

With regard to claims 8 and 9, Hermann teaches monitoring fluorescence at 0.1 C/s increments (see page 427, column 1) which encompasses monitoring at longer increments.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the confirmatory melting temperature analysis method of Herrmann with the PCR method of Wittwer since Hermann states "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)." Thus, an ordinary practitioner would have been motivated to confirm the PCR analysis of Wittwer with a melting point analysis of Hermann in order to perform a variety of

checks, including multiplex genotyping, internal controls and internal competitors as standards. Further, it would have been prima facie obvious to combine Hermann with any analytical PCR method to improve the specificity and validity of the method for the reasons cited from the Hermann paper. This additional verification solves the problem, recognized by Wittwer that " accurately discriminating between positive and negative samples is not easy in practice (see column 7, lines 23-24)" The specification continues, noting "Automatic identification of the background is surprisingly difficult. (see column 7, paragraph 0027)." Hermann provides one solution for this problem by providing a means to accurately discriminate between positive and negative PCR samples such as those used by Wittwer which would further support the determination made by the analytical method of Wittwer.

Response to Arguments

7. Applicant's arguments filed April 12, 2005 have been fully considered but they are not persuasive.

With respect to the double patenting rejection, Applicant attempts to parse the prior art into the least interpretable unit by arguing that there is a contrast between the method taught in the claims of U.S. Patent No. 6,387,621 and the method of Hermann. Specifically, Applicant argues that the claims of U.S. Patent No. 6,387,621 determine the presence of a nucleic acid without comparison to other nucleic acids while Hermann compares signals from different nucleic acids. Applicant then argues that Hermann is limited to the use of a melting curve analysis in analyzing multiple DNAs and not the single DNA used in the claims of U.S. Patent No. 6,387,621.

Applicant's argument is both incorrect and unnecessarily complex. The argument is incorrect because Hermann imposes no limitation on the melting curve analysis which requires it to compare the results of different nucleic acids. Hermann recognizes that "Probes of a single color are usually used for genotyping (see page 425, column 2)." This clearly demonstrates that Hermann was aware that a single nucleic acid could be analyzed. Further, while it is true that Hermann is focused on allele comparisons, it is equally clear that the claims of U.S. Patent No. 6,387,621 also teach allele comparisons. For example, claim 11 states "The method of claim 9 wherein the nucleic acid is further analyzed to determine the presence of a particular allele." Consequently, Applicant incorrectly attempts to limit the teaching of Hermann to multiple nucleic acids when he teaches both single and multiple nucleic acid probes and Applicant incorrectly limits the claims of U.S. Patent No. 6,387,621 when claim 11 clearly teaches comparison of alleles, a comparison of multiple nucleic acids.

The combination of the claims of U.S. Patent No. 6,387,621 and Hermann is based upon a simply premise, that Hermann's teaching that temperature melting can be confirmatory of successful or unsuccessful PCR methods is desirably combined with the claims of U.S. Patent No. 6,387,621 to determine whether that method is successful. Hermann expressly teaches that the temperature melting method can be used as a confirmatory control, as already quoted in the rejection above "The ability to multiplex PCR analysis by color and Tm has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target

amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)."

Consequently, Applicant's arguments are based on a faulty premise regarding the teachings of Hermann, Wittwer and the claims of U.S. Patent No. 6,387,621. Finally, as previously discussed, an obviousnes rejection requires a suggestion and motivation to combine, not anticipation of the invention. In Ruiz v. A.B. Chance Company, (Fed. Cir. 2004), heard on an appeal after remand, the Federal Circuit noted " While this court indeed warns against employing hindsight, its counsel is just that – a warning. That warning does not provide a rule of law that an express, written motivation to combine must appear in prior art references before a finding of obviousness. Stated differently, this court has consistently stated that a court or examiner may find a motivation to combine prior art references in the nature of the problem to be solved. " In the current case, the motivation derives from both bases cited by the Federal Circuit. There is strong direct motivation from Hermann to use the melting temperature method to control for variation, particularly in combination with the allelic analysis method of claim 11 of U.S. Patent 6,387,621. Also, the nature of the recognized problem in U.S. Patent No. 6,387,621 lends itself to solution by combination with the Hermann reference. So on both grounds, motivation is present. Therefore, the obviousness type double patenting rejection is maintained.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
5/18/05